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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/879,442	06/11/2001	Vincent Dubois	MXI-321CP	3549

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EXAMINER	
KOSAR, ANDREW D	
ART UNIT	PAPER NUMBER
1654	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	01/17/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

T4

Office Action Summary	Application No.	Applicant(s)	
	09/879,442	DUBOIS ET AL.	
	Examiner	Art Unit	
	Andrew D. Kosar	1654	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 October 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *2,3,5-21,23-30,37,118-120 and 122-125* is/are pending in the application.

4a) Of the above claim(s) *9,10,12,20,21 and 27* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *2,3,5-8,11,13-19,23-26,28-30,37,118-120 and 122-125* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *11 June 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Response to Arguments/Amendments

Applicant's amendments and arguments filed October 5, 2006 are acknowledged and have been fully considered. Any rejection and/or objection not specifically addressed is herein withdrawn.

Claims 2, 3, 5-21, 23-30, 37, 118-120 and 122-125 are pending. Claims 9, 10, 12, 20, 21 and 27 remain withdrawn for the reasons of record.

Claims 2, 3, 5-9, 11, 13-19, 23-26, 28-30, 37, 118-120 and 122-124 and new claim 125 have been examined on the merits.

Applicant's have amended the claims and thus the rejection of claims 2, 3, 5-8, 11, 14-16, 18, 19, 23-26, 30, 37, 122 and 123 under 35 USC § 102(e) (as anticipated by Garksy) and the rejection of claims 4-8, 11, 13-17, 19, 25, 26, 30 and 118 under 35 USC § 103(a) (as obvious over Trouet in view of Veronese, Dalborg, Gaetner and Inada) are withdrawn.

Applicant has provided a statement of common ownership with regards to Application 10/311,411 (page 15, *Remarks*, 10/5/06).

In turning to the outstanding rejections, the primary reference(s) relied upon under 35 USC § 103(a) and under Double Patenting are the International Application (PCT) and corresponding US Patent, issued therefrom (collectively referred to as "Trouet et al." by Applicant). In as much as Applicant has argued the references collectively, the examiner will address the traversal in kind.

Applicant argues individually against each of the secondary references in the combination, arguing that the art lacks motivation to combine the references because (1) Trout

teaches that the prodrug remains stable in the serum and blood and are insensitive to the action of circulating proteinases and peptidases associated with red cells and that (2) Trout does not indicate that the prodrug was unstable.

Applicant further argues that the references regarding solubility, hydrophobicity and mass spectroscopy are improperly relied upon because the prodrugs are already soluble and small peptides and the reference deals primarily with large proteins and the reference with hydrophobicity deals with carbohydrates. Applicant argues that the MS reference deals primarily with proteins of an undetermined structure. With regards to the elected species, these arguments in this aspect only have been found persuasive and are no longer relied upon.

With regards to items (1) and (2), the examiner respectfully disagrees. Although Applicant has provided results in the specification that the toxicity is reduced (as discussed in the remarks spanning pages 13 and 14), Applicant arguments are not persuasive. The fact that applicant has recognized another advantage which would flow naturally from following the suggestion of the prior art cannot be the basis for patentability when the differences would otherwise be obvious. See *Ex parte Obiaya*, 227 USPQ 58, 60 (Bd. Pat. App. & Inter. 1985).

Applicant argues that the compounds of Trouet were insensitive to proteinases and are stable and that such a teachings would not provide motivation for N-succinylating the peptide, however, contrary to the excerpt Applicant cites (column 8, lines 41-44), Trouet also states that stability is, "less than 20%, and preferably less than 2%, of the compound is cleaved by said enzymes during its storage in human blood at 37 °C for more than 2 hours." (column 3, lines 7-10). One would have gleaned from this section ample motivation to look for additional stabilization of the compounds of Trouet. The rejections are maintained and set forth below.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 2, 3, 5-8, 11, 13-19, 23-26, 28-30, 37, 118-120 and 122-125 remain/are rejected under 35 U.S.C. 103(a) as being unpatentable over TROUET (WO 96/05863 A1; F14: PTO-1449 of 11/30/01 – considered with English equivalent provided by Applicant 11/4/04, *see Page 4 Office Action mailed 11/4/04*) in view of LI (PTO-892, 11/4/04), HOLCENBERG (PTO-892, 4/5/06), HALL (PTO-892, 4/5/06), GUTHEIL (PTO-892, 4/5/06) and/or LaROCHELLE (PTO-892, 4/5/06).

The instant claims are drawn generally to compositions of the formula:

[negatively charged protecting group]-$(aa)_n$X-$(aa)_3$-[therapeutic agent], where X is a non-genetically encoded amino acid, e.g. βAla, D-Ala, 2-Nal, n is 0-16 and each aa is any amino acid. The compound must be cleavable by TOP.

Trouet teaches βAla-Leu-Ala-Leu-(Dox/Dnr) (table 1, page 25). Trouet teaches the compounds as pharmaceutical compositions (e.g. Figures 20 and 21).

Li teaches succinylation of ACTH, and that succinylation reduced the number of trypsin cleavage products (e.g. Figure 3, page 2639) and further teaches that glucagon, prolactin,

lysozyme and ribonuclease have been succinylated and that the products, "are completely soluble in aqueous solution of a pH above 5" (page 2640).

Holcenberg (cited by Katre) teaches succinylation of glutaminase-asparaginase and that, "These modifications markedly prolonged the half-lives of the enzyme in mice, rats, and rabbits. [...] Succinylation protected the enzyme from trypsin digestion." (*Summary*, page 4165).

Gutheil and Hall are provided for the beneficial teachings that succinyl and other dicarboxylic acid moieties are well known in the art as amino acid protecting groups (Gutheil- column 9; Hall, column 3). Gutheil teaches that the protecting group, "protect the reactive functional group from undesirable chemical reactions."

LaRochelle is provided for the beneficial teachings that pharmaceutical compositions formulation is routine in the art (e.g. column 10, lines 39-59, citing *Remington's*).

The difference between Trouet and the instant claims, is that while Trouet teaches the core βAla-Leu-Ala-Leu-(Dox/Dnr), Trouet does not teach succinylated βAla-Leu-Ala-Leu-(Dox/Dnr).

It would have been obvious at the time of the invention to have succinylated βAla-Leu-Ala-Leu-(Dox/Dnr) in order to protect it from 'undesirable reactions' such as trypsin digestion *in vivo* and to formulate it in a pharmaceutical with a carrier.

One would have been motivated to have succinylated βAla-Leu-Ala-Leu-(Dox/Dnr) in order to reduce the undesirable trypsin digestion *in vivo*, as taught by the references above.

One would have had a reasonable expectation for success in succinylating βAla-Leu-Ala-Leu-(Dox/Dnr) and thereby reducing the undesirable trypsin digestion *in vivo*, as succinylation is a routinely practiced technique in the peptide arts.

One would have been motivated to make the succinylated composition into a pharmaceutical in order to compare the succinylated product to the free form and determine to what extent the *in vivo* stability had been modified.

One would have had a reasonable expectation for success in making the compound into a pharmaceutical composition, as pharmaceutical compositions are routinely prepared in the medicinal arts, and because Trouet teaches the core βAla-Leu-Ala-Leu-(Dox/Dnr) in pharmaceuticals.

From the teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Claims 2, 3, 5-8, 11, 13-19, 23-26, 28-30, 37, 118-120 and 122-125 remain/are rejected under 35 U.S.C. 103(a) as being obvious over TROUET (US Patent 5,962,216; F13: PTO-1449 of 11/30/01) in view of LI (PTO-892, 11/4/04), HOLCENBERG (PTO-892, 4/5/06), HALL (PTO-892, 4/5/06), GUTHEIL (PTO-892, 4/5/06) and/or LaROCHELLE (PTO-892, 4/5/06).

The applied reference has a common inventor with the instant application. Based upon the earlier effective U.S. filing date of the reference, it constitutes prior art only under 35 U.S.C. 102(e). This rejection under 35 U.S.C. 103(a) might be overcome by:

(1) a showing under 37 CFR 1.132 that any invention disclosed but not claimed in the reference was derived from the inventor of this application and is thus not an invention "by another";

(2) a showing of a date of invention for the claimed subject matter of the application which corresponds to subject matter disclosed but not claimed in the reference, prior to the effective U.S. filing date of the reference under 37 CFR 1.131;

(3) an oath or declaration under 37 CFR 1.130 stating that the application and reference are currently owned by the same party and that the inventor named in the application is

the prior inventor under 35 U.S.C. 104, together with a terminal disclaimer in accordance with 37 CFR 1.321(c); or
(4) showing that the reference is disqualified under 35 U.S.C. 103(c) as prior art in a rejection under 35 U.S.C. 103(a). *See MPEP § 706.02(l)(1) and § 706.02(l)(2).*

The instant claims are presented *supra*. The teachings of Li, Holcenberg, Gutheil, Hall and LaRochelle are presented *supra*.

Trouet teaches βAla-Leu-Ala-Leu-(Dox/Dnr) (e.g. claims 3; SEQ ID NOs:1, 2; Table 1, column 13). Trouet teaches the compounds as pharmaceutical compositions (e.g. Figures 20 and 21; column 18, lines 17-20).

It would have been obvious at the time of the invention to have succinylated βAla-Leu-Ala-Leu-(Dox/Dnr) in order to protect it from 'undesirable reactions' such as trypsin digestion *in vivo* and to formulate it in a pharmaceutical with a carrier.

One would have been motivated to have succinylated βAla-Leu-Ala-Leu-(Dox/Dnr) in order to reduce the undesirable trypsin digestion *in vivo*, as taught by the references above.

One would have had a reasonable expectation for success in succinylating βAla-Leu-Ala-Leu-(Dox/Dnr) and thereby reducing the undesirable trypsin digestion *in vivo*, as succinylation is a routinely practiced technique in the peptide arts.

One would have been motivated to make the succinylated composition into a pharmaceutical in order to compare the succinylated product to the free form and determine to what extent the *in vivo* stability had been modified.

One would have had a reasonable expectation for success in making the compound into a pharmaceutical composition, as pharmaceutical compositions are routinely prepared in the medicinal arts, and because Trouet teaches the core βAla-Leu-Ala-Leu-(Dox/Dnr) in pharmaceuticals.

From the teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 2, 3, 5-8, 11, 13-19, 23-26, 28-30, 37, 118, 119, 120 and 122-124 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-19, 25-37 and 40-42 of TROUET(US Patent 5,962,216; F13: PTO-1449 of 11/30/01) in view of Li, DeJongh, Katre, Kilbanov, Holcenberg, Gutheil and LaRochelle.

The teachings of Trouet, Li, DeJongh, Katre, Kilbanov, Holcenberg, Gutheil and LaRochelle are presented *supra*.

Trouet teaches βAla-Leu-Ala-Leu-Dox (claims 3). Trouet teaches the compounds as pharmaceutical compositions (claims 19 and 37).

In looking to the specification for definitions and support for the products claimed beyond βAla-Leu-Ala-Leu-Dox, the specifically contemplated embodiments which provide support for the claims are found within the examples and tables, e.g. Table 1 and Examples 1-14, which include the Dnr conjugate.

It would have been obvious at the time of the invention to have succinylated βAla-Leu-Ala-Leu-(Dox/Dnr) in order to protect it from 'undesirable reactions' such as trypsin digestion *in vivo* and to formulate it in a pharmaceutical with a carrier.

One would have been motivated to have succinylated βAla-Leu-Ala-Leu-(Dox/Dnr) in order to reduce the undesirable trypsin digestion *in vivo*, as taught by the references above.

One would have had a reasonable expectation for success in succinylating βAla-Leu-Ala-Leu-(Dox/Dnr) and thereby reducing the undesirable trypsin digestion *in vivo*, as succinylation is a routinely practiced technique in the peptide arts.

One would have been motivated to make the succinylated composition into a pharmaceutical in order to compare the succinylated product to the free form and determine to what extent the *in vivo* stability had been modified.

One would have had a reasonable expectation for success in making the compound into a pharmaceutical composition, as pharmaceutical compositions are routinely prepared in the medicinal arts, and because Trouet teaches the core βAla-Leu-Ala-Leu-(Dox/Dnr) in pharmaceuticals.

From the teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Claims 2, 3, 5-12, 14, 15, 17-19, 21, 23-27, 30, 37 and 122-124 remain provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1, 4-8, 11, 13-18, 23-29, 57, 58, 60, 61 and 63 of copending Application No. 10/311,411 (PICKFORD). This rejection was previously set forth in view of the amendments filed January 6, 2006 in Pickford and has been updated to reflect Applicant's allowed claims of April 14, 2006.

Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims are of an overlapping scope, both being generally drawn to stabilizer-peptide-therapeutic conjugates and pharmaceutical compositions, thereof.

Furthermore, the compounds claimed by Pickford are species of the instant claims, e.g. claim 23 of Pickford. Further, the compounds of Pickford need only be cleavable by another enzyme, but does not require that the compounds are not cleavable by TOP, and thus the compounds of Pickford either anticipate, or are anticipated by, the instant claims.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented. Please note, upon issuance of a Patent Number this rejection will be maintained as a non-provisional nonstatutory obviousness-type double patenting.

Applicant's willingness to consider filing a terminal disclaimer if and/or when appropriate (*Remarks, page 15*) is noted.

Conclusion

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

ISAACS (US Patent 6,265,540) teaches protecting groups of peptides are well known in the art to include, e.g. succinyl, glutaryl and "many others known in the art".

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

This application contains claims 9, 10, 12, 20, 21 and 27 drawn to an invention nonelected with traverse on August 26, 2004. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Andrew D. Kosar whose telephone number is (571)272-0913. The examiner can normally be reached on Monday - Friday 08:00 - 16:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Cecilia J. Tsang can be reached on (571)272-0562. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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